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AUTHOR(S):

KOBAYASHI, Yutaka; TERAMURA, Fumio; MIKAWA,
Haruki; AKAISHI, Kyoji; FUKUDA, Hiroshi

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STUDIES ON THE CHANGE OF TUBERCULIN REACTION REPEATEDLY EXAMINED AT THE SAME SITE OF THE SKIN OF A BCG VACCINATED GROUP OF SCHOOL CHILDREN

2. RESULTS OBTAINED 6 AND 12 MONTHS AFTER BCG VACCINATION, ESPECIALLY "L" REACTION

Yutaka KOBAYASHI, Fumio TERAMURA, Haruki MIKAWA*,

小林 裕 寺 村 文 男 三 河 春 樹

Kyoji AKAISHI* and Hiroshi FUKUDA*

赤 石 強 司 福 田 潤

*Division of Pediatrics of the Tuberculosis Research Institute,
Kyoto University and* the Department of Pediatrics,
Medical Faculty, Kyoto University*

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Introduction

In the previous report¹⁾, it was mentioned that the accelerated and augmented reaction was caused by the second tuberculin test (the first repetition) on the same site of the skin. Moreover, the change of the color tone of the tuberculin reaction at 48 hour value has recently been noticed especially in the cases in which the tuberculin tests were frequently repeated and this change of color tone was named as "L" reaction by Saito et al.²⁾. Maeda³⁾ named this color tone as "K" reaction.

The present investigation was undertaken to answer the question whether the grade of accelerated and augmented reaction might be changed or not by the additional tuberculin tests and what kind of relation might exist between the change of color tone and the repetition of tuberculin test. In addition, the side effect of BCG at the vaccinated site is reported.

Materials and Methods

BCG vaccinated children in the previous report¹⁾ were tuberculin tested at 6 and 12 months after the vaccination. Six months after vaccination the tuberculin test was done at the same site of the left forearm as in the previous report and 3 cm distal part of the right forearm from the elbow. Twelve months after vaccination the tuberculin test was again done at the same site of the left forearm and 8 cm proximal part of the flexor side of the right upper arm from the elbow (see Fig. 1).

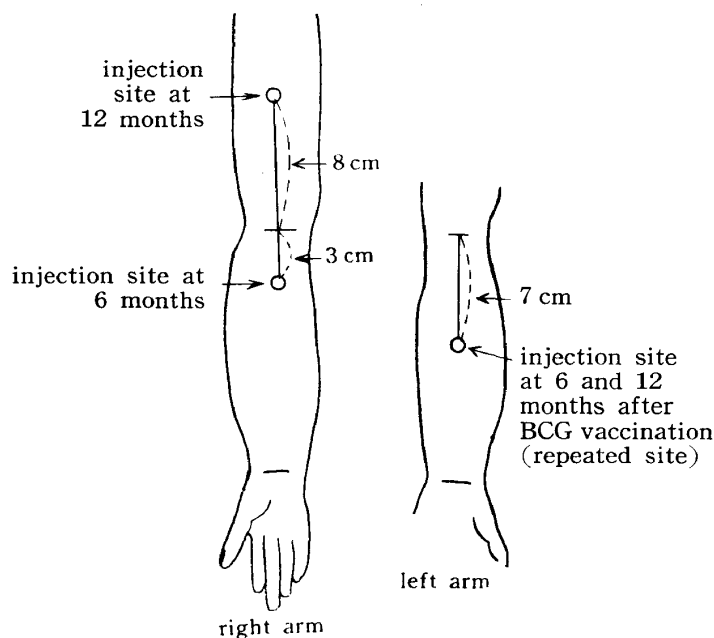


Fig. 1. Injection sites of tuberculin.

The tuberculin test done on the flexor side of the upper arm may be regarded as equivalent to that of the forearm by Honzawa⁴⁾ and Shioda⁵⁾.

Since the tuberculin test done at the left forearm 3 months after vaccination was designated as the first repetition in the previous report¹⁾, the tests done at the same site 6 and 12 months after vaccination in this report are designated as the second and the third repetition, respectively.

Because the children of the sixth grade finished their course and entered the middle school 10 months after BCG vaccination, the number of children was 251 in sixth month after vaccination but was 203 after 12th month.

Ten tuberculous patients were tuberculin tested at the middle parts of the flexor sides of both forearms and were read every 24 hours for 7 days.

Old tuberculin used and its dilution method and the reading index are the same as reported in the previous report¹⁾.

Results

1) Accelerated and augmented reaction

Table 1 shows the results of 6 months after BCG vaccination. Table 1 (a) and (b) show the difference between 24 and 48 hour values of the new (a) and the repeated (b) sites. In the Table 1 (a) it is shown that at the new site 65 cases were stronger at 48 hour value than at 24 hour and 33 cases were the reverse, indicating the increase of the reaction with lapse of time between 24

Table 1. Tuberculin reaction, 6 months after BCG vaccination.

(a) Comparison of 24 and 48 hour values in new site.

48 hr. 24 hr.	—	±	+	++	+++	No. of 48 hr. > 24 hr.
—	29	8	3	2	0	65
±	12	25	9	21	0	
+	2	3	24	22	0	
++	0	6	10	75	0	
+++	0	0	0	0	0	
No. of 24 hr. > 48 hr.	33					

(c) Comparison of injection sites at 24 hour value.

new re- peated	—	±	+	++	+++	No. of new > repeated
—	1	0	0	0	0	0
±	1	1	0	0	0	
+	9	15	6	0	0	
++	31	50	44	86	0	
+++	0	1	1	5	0	
No. of repeated > new	157					

(b) Comparison of 24 and 48 hour values in repeated site.

48 hr. 24 hr.	—	±	+	++	+++	No. of 48 hr. > 24 hr.
—	1	0	0	0	0	2
±	1	0	0	1	0	
+	4	6	19	1	0	
++	4	12	121	74	0	
+++	0	0	4	3	0	
No. of 24 hr. > 48 hr.	155					

(d) Comparison of injection sites at 48 hour value.

new re- peated	—	±	+	++	+++	No. of new > repeated
—	5	2	1	2	0	81
±	3	6	5	4	0	
+	24	24	29	67	0	
++	11	10	11	47	0	
+++	0	0	0	0	0	
No. of repeated > new	83					

and 48 hours, although the stronger cases at 24 hour value increased in number compared to the results obtained 3 months after BCG vaccination¹⁾. On the contrary, at the repeated site the number of cases in which 48 hour values were stronger than 24 hour was two and the reverse was 155 as seen in Table 1 (b), indicating clearly the stronger reaction at 24 hour than at 48 hour; that is, the accelerated reaction was also observed. When the reactions were compared between the new and repeated sites at 24 hour (Table 1 (c)) the reaction was clearly stronger at the repeated site (157 cases) than at the new site (no case). But at 48 hour the difference became obscure as seen in Table 1 (d).

Table 2 shows the results 12 months after BCG vaccination, indicating the similar tendency as seen in Table 1.

Table 2. Tuberculin reaction, 12 months after BCG vaccination.

(a) Comparison of 24 and 48 hour values in new site.

48 hr. 24 hr.	—	±	+	++	+++	No. of 48 hr. > 24 hr.
—	11	7	1	4	0	39
±	18	29	6	16	0	
+	0	0	3	4	0	
++	3	4	4	92	1	
+++	0	0	0	0	0	
No. of 24 hr. > 48 hr.	29					

(c) Comparison of injection sites at 24 hour value.

new re- peated	—	±	+	++	+++	No. of new > repeated
—	1	0	0	0	0	5
±	1	2	0	1	0	
+	5	7	3	4	0	
++	16	59	4	91	0	
+++	0	1	0	8	0	
No. of repeated > new	101					

(b) Comparison of 24 and 48 hour values in repeated site.

48 hr. 24 hr.	—	±	+	++	+++	No. of 48 hr. > 24 hr.
—	1	0	0	0	0	3
±	2	2	0	0	0	
+	2	2	12	3	0	
++	1	13	83	73	0	
+++	0	0	4	5	0	
No. of 24 hr. > 48 hr.	112					

(d) Comparison of injection sites at 48 hour value.

new re- peated	—	±	+	++	+++	No. of new > repeated
—	4	2	0	0	0	63
±	5	6	0	5	0	
+	14	18	12	55	0	
++	9	13	2	57	1	
+++	0	0	0	0	0	
No. of repeated > new	56					

The diameters of redness were measured as done in the previous report¹⁾. Six months after BCG vaccination 48 hour values were usually larger than 24 hour at the new site (Fig. 2), but the dots more closely distributed around the diagonal line compared to the results of the new sites obtained at 1 and 3 months after vaccination¹⁾; that is, the difference between 24 and 48 hour value became smaller. On the contrary, Fig. 3 shows that 24 hour values were remarkably larger than 48 hour at the repeated site. And at 24 hour the values of the repeated site were remarkably larger than those of the new site (Fig. 4), similar as the results 3 months after vaccination. Fig. 5 shows the comparison of the new site to the repeated site at 48 hour value: the cases of new <repeated were 170 and new > repeated were 70, while the cases of new <repeated were 96 and new > repeated were 142 in 3 months after vaccination of the previous report¹⁾. But, when the larger diameter at either 24 or 48 hour in each site was adopted

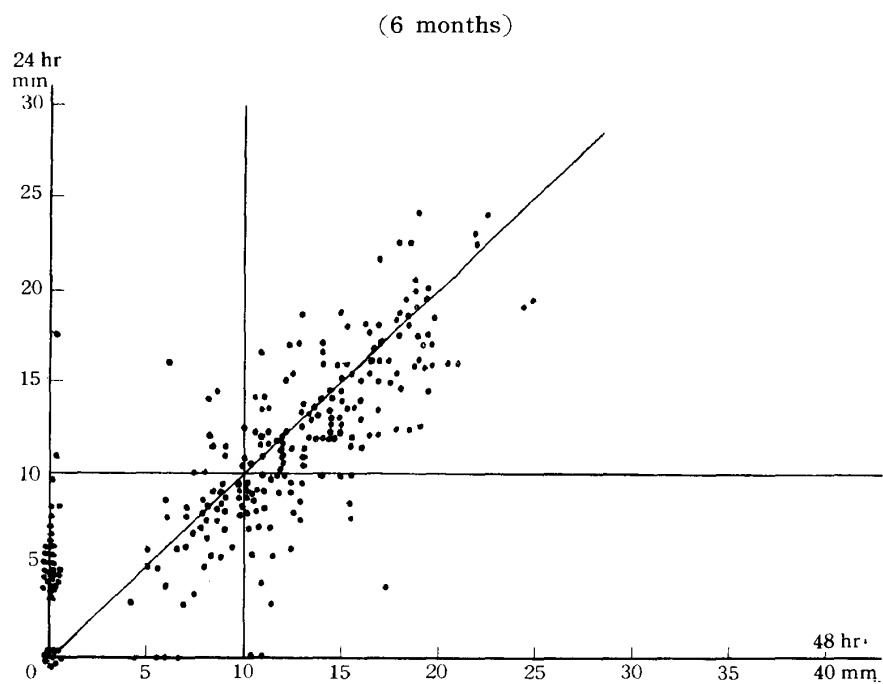


Fig. 2. Comparison of 24 and 48 hour values in redness in new site.

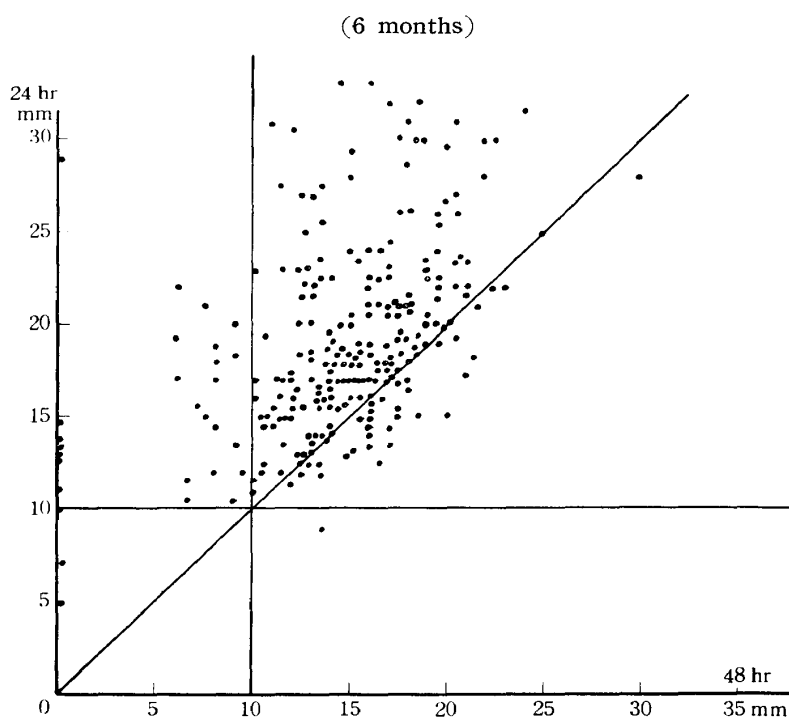


Fig. 3. Comparison of 24 and 48 hour values in redness in repeated site.

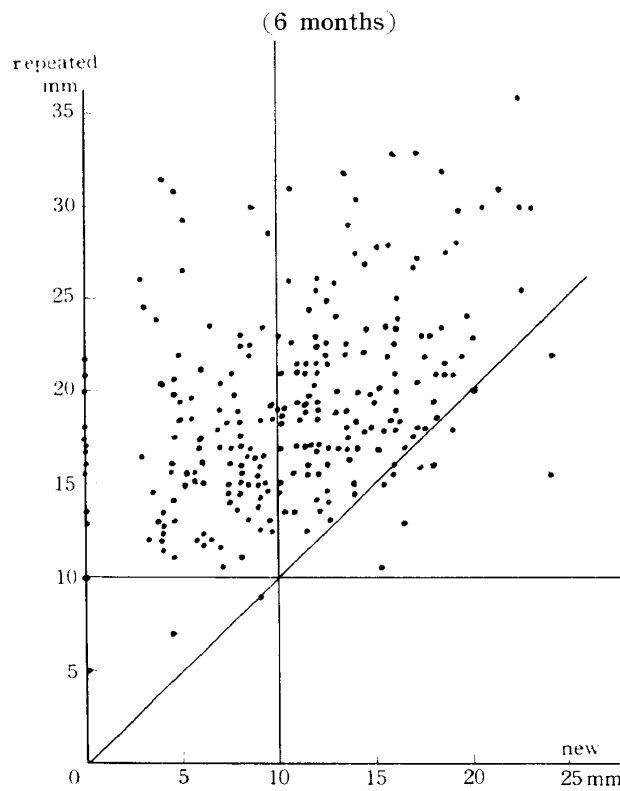


Fig. 4. Comparison of injection sites in redness at 24 hour value.

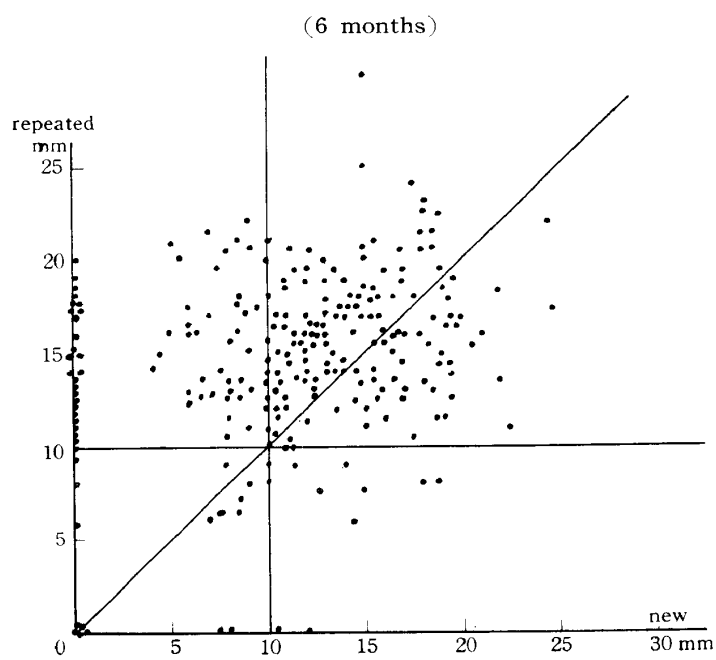


Fig. 5. Comparison of injection sites in redness at 48 hour value.

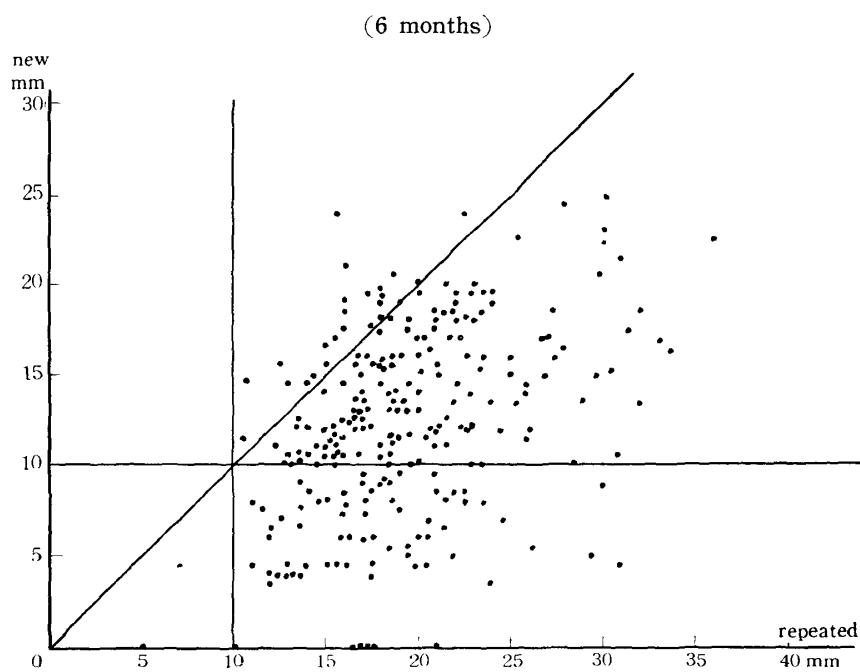


Fig. 6. Comparison of injection sites in redness, when the larger diameter at either 24 or 48 hours is adopted.

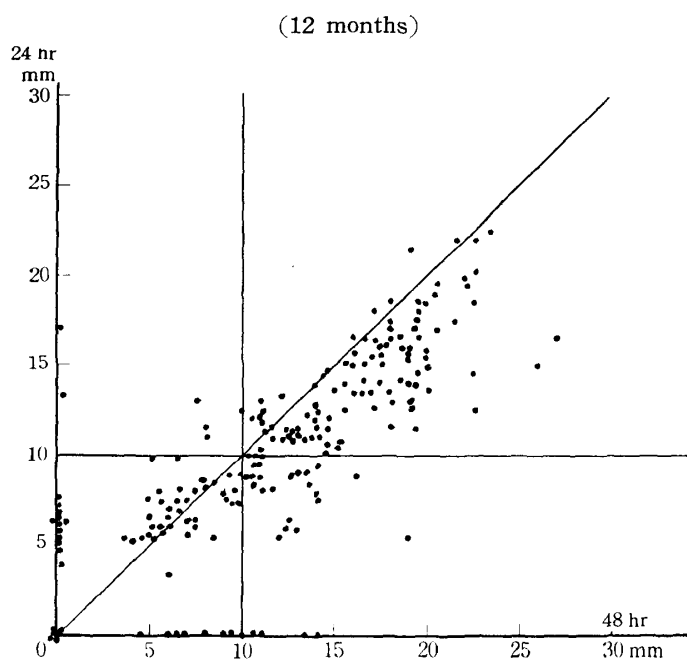


Fig. 7. Comparison of 24 and 48 hour values in redness in new site.

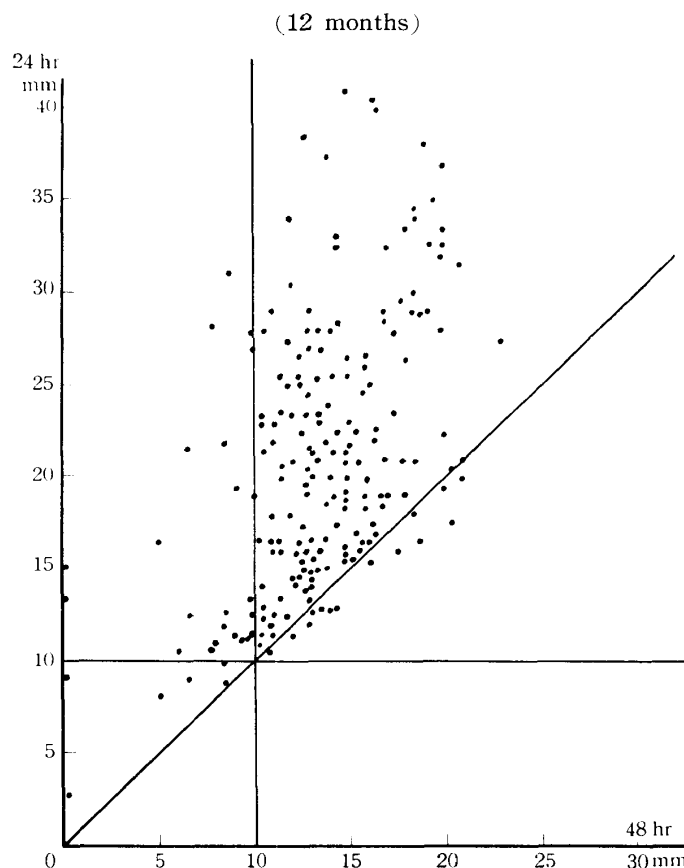


Fig. 8. Comparison of 24 and 48 hour values in redness in repeated site.

(Fig. 6), the result of 6 months was similar as that of 3 months after vaccination¹⁾.

Fig. 7, 8, 9, 10 and 11 show the results of observations 12 months after BCG vaccination.

When the diameter of redness of 24 hour value was compared to 48 hour at the new (Fig. 7) and repeated (Fig. 8) sites, the results were similar as those of 6 months after vaccination (Fig. 2 and 3). At 24 hour the values of the repeated site were remarkably larger than those of the new site (Fig. 9). At 48 hour the values of the repeated site were still larger than the new site (Fig. 10). When the larger diameter at either 24 or 48 hour in each site was adopted (Fig. 11), the values of the repeated site were remarkably larger than those of the new site, therefore, the augmented reaction was also observed in 6 and 12 months after vaccination.

Moreover, it should be mentioned that in 12 months after vaccination, although the number of children tested decreased, the number of cases of which the reactions of the new site were larger than the repeated site did not change and the cases of the repeated site $>$ new site decreased.

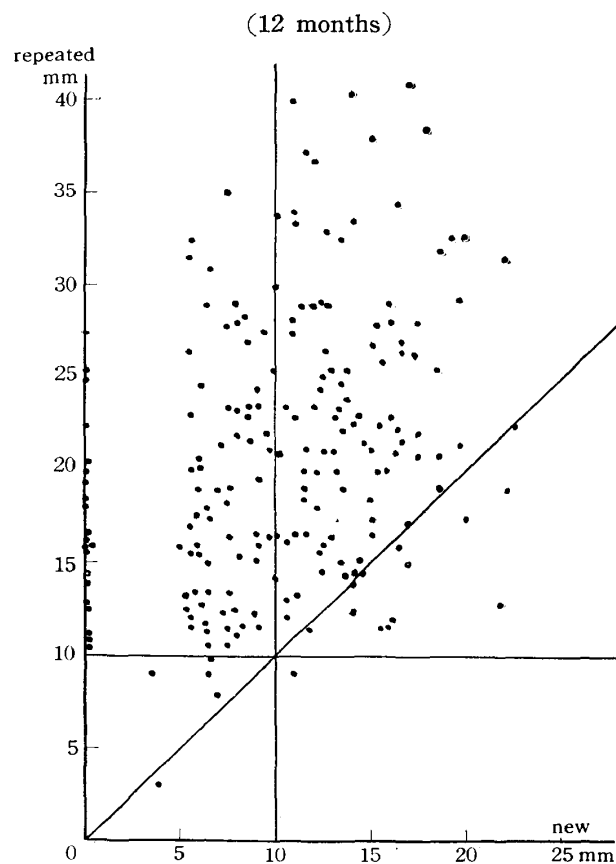


Fig. 9. Comparison of injection sites in redness at 24 hour value.

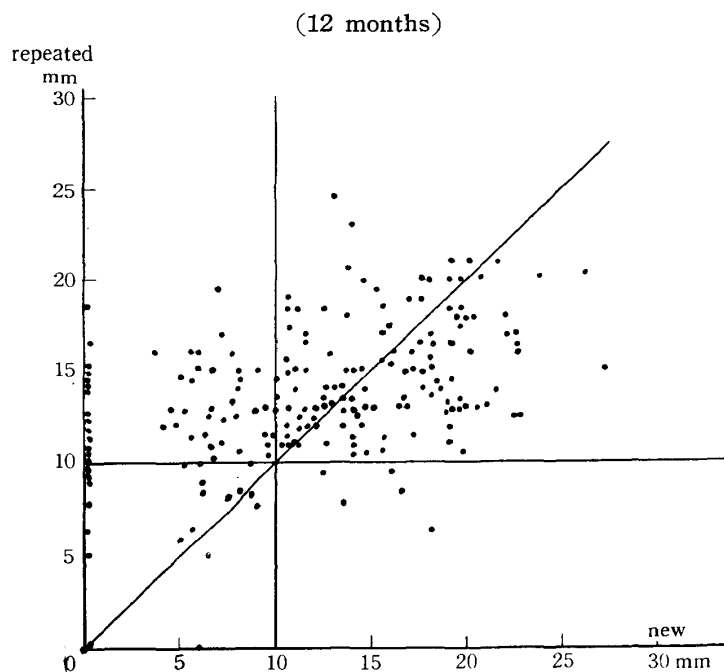


Fig. 10. Comparison of injection sites in redness at 48 hour value.

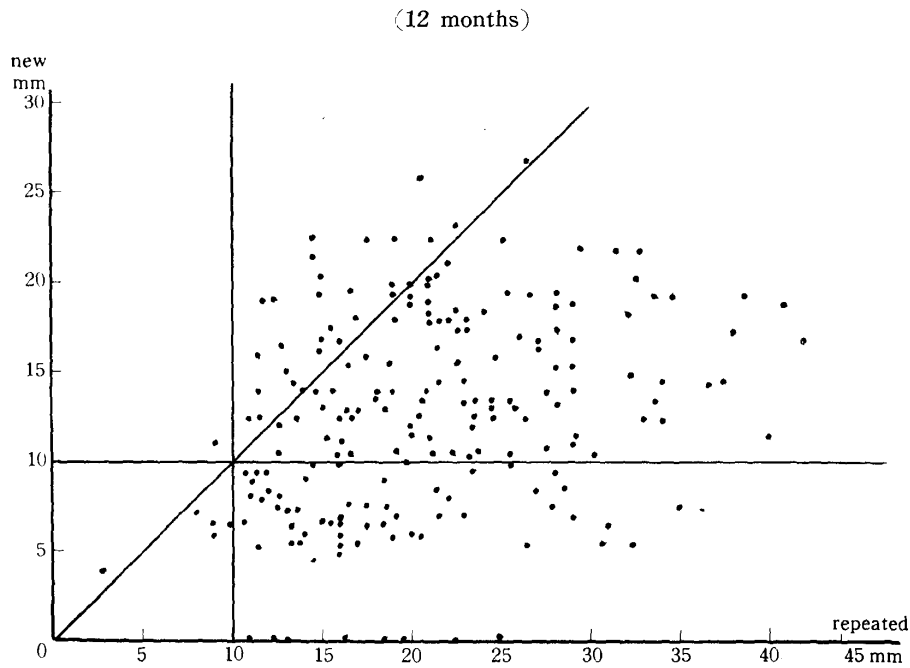


Fig. 11. Comparison of injection site in redness, when the larger diameter at either 24 or 48 hours is adopted.

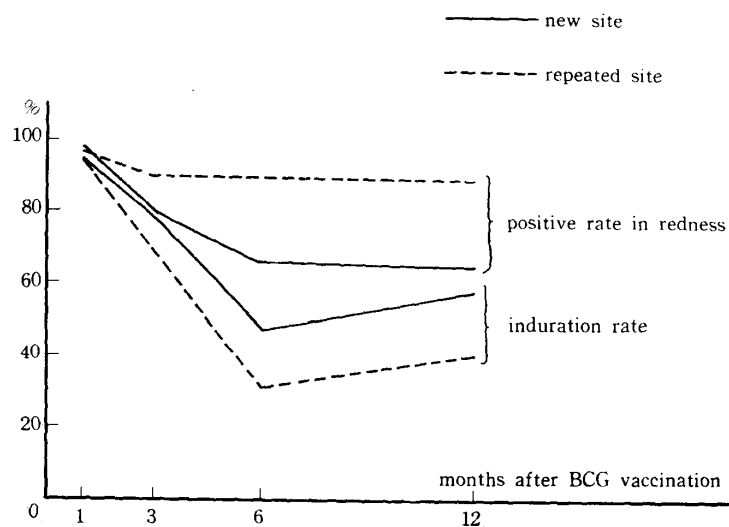


Fig. 12. The percentage of tuberculin reaction after BCG vaccination.

Fig. 12 shows the positive rate in redness and the induration rate of the 48 hour readings, when the tuberculin tests were repeated at the same site (dotted lines) and were done at the new sites. The positive rate was lower but the induration rate was conversely higher at the new site than at the repeated site.

2) "L" reaction

The reaction of which color tone was not fresh red as had formerly been seen but livid red, pale brown or only pigmentated and so on and the margin of the reacted area was not usually discernible from the unreacted area was named as "L" reaction as mentioned above.

Table 3 shows the number of cases observed "L" color tone in the positive

Table 3. "L" reaction in new and repeated sites.

Injection sites	Tuberculin reaction Months after BCG vaccination	No. of positive		No. of positive	
		reaction without induration (+)	No. of reaction with "L" color tone in (+)	reaction with induration (++)	No. of reaction with "L" color tone in (++)
new site (right arm)	1	3	1	217	1
	1*	6	1	214	0
	3	3	0	194	0
	6	46	11	120	2
	12	14	0	116	0
repeated site (left arm)	3	49	43	177	57
	6	144	143	79	69
	12	99	99	81	72

* Results in 1 month after BCG vaccination in left forearm.

Note: 251 cases were examined in 1, 3 and 6 months and 203 cases in 12 months after BCG vaccination.

reactors at 48 hour 1, 3, 6 and 12 months after BCG vaccination. The results in the left forearm 1 month after vaccination (marked with asterisk) are thought to be the new site as mentioned in the previous report¹⁾. As seen in Table 3, the cases which showed "L" color tone were much more in number at the repeated sites than at the new sites.

Fig. 13 shows the appearance rate of "L" reaction at the repeated site. In the figure, the shaded portion above the induration rate curve, (a), shows the "L" color tone without induration and the shaded portion under the induration rate curve, (b), shows "L" color tone with induration. It is seen that most of the reaction done on and after the second repetition (6 and 12 months) present "L" color tone.

Table 4 shows the results of the tuberculin test of 10 tuberculous patients at the middle parts of flexor sides of both forearms and read every 24 hours for 7 days. The injection site of left forearm was the part which the tuberculin tests had been usually repeated by this time, while the site of right forearm was the new site. None of the cases was less than 10 mm in diameter of redness

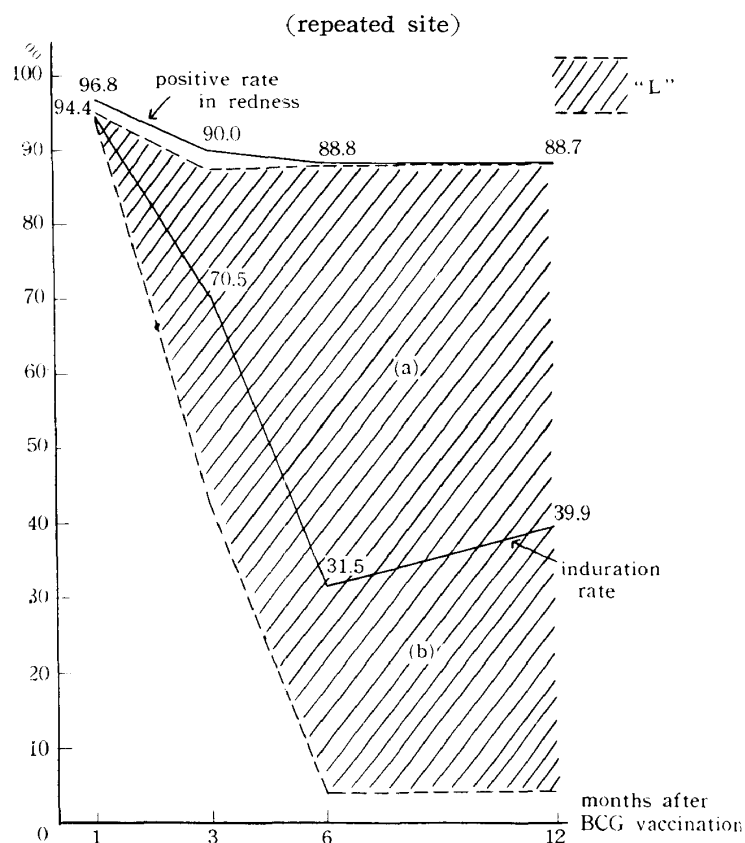


Fig. 13. The appearance of "L" reaction by repetition of tuberculin reaction.

Table 4. The process of tuberculin reaction and "L" color tone in new (right forearm) and repeated (left forearm) sites of 10 tuberculous patients.

right forearm	days after tuberculin injection	1	2	3	4	5	6	7
	No. of double redness	6	9	4	2	1	0	0
	No. of redness with induration	4	1	6	8	9	9	6
	No. of redness alone	0	0	0	0	0	1	4
	No. of "L" color tone	0	0	0	0	3	5	8
left forearm	days after tuberculin injection	1	2	3	4	5	6	7
	No. of double redness	4	2	0	0	0	0	0
	No. of redness with induration	5	7	7	7	4	2	2
	No. of redness alone	1	1	3	3	6	8	8
	No. of "L" color tone	1	4	6	9	9	10	10

for 7 days at the both sites. In the right forearm, 6 cases showed double redness and 4 cases redness with induration at 24 hour. At 48 hour the reaction increased generally — 9 cases showed double redness — and then decreased gradually. At the 7th day 6 cases showed redness with induration and 4 cases redness alone. “L” color tone appeared at the 5th day in 3 cases and then increased with the decrease of tuberculin reaction. In the left forearm (repeated site) 4 cases showed double redness, 5 cases redness with induration and 1 case redness alone at 24 hour and then the reaction decreased; that is, 2 cases at 48 hour and none at 72 hour showed double redness.

With the lapse of time the induration disappeared gradually and the cases of redness alone increased: 3 cases at 72 hour, 6 at the 5th day and 8 at the 6th day. “L” color tone increased as well: 6 cases at 72 hour and 9 at the 4th day presented “L” color tone. Therefore, it may be said that the appearance of “L” color tone is brought about just before the disappearance of the tuberculin reaction.

3) The local reaction at the BCG vaccinated site

The BCG vaccinated site was observed simultaneously with the readings of the tuberculin reaction 1, 3 and 6 months after vaccination. The diameters were measured classifying into induration, pustule, ulcer, crust and scar (Table 5),

Table 5. Local reaction at the site of BCG vaccination.
(251 cases)

Time	Local reaction	Induration	Pustule	Ulcer and crust	Scar	Total
	Diameter					
1 month after vaccination	< 5 mm	1	0	1	18	20
	6~9 mm	0	34	106	38	178
	>10 mm	0	12	40	1	53
	total {	1	46	147	57	251
	% {	0.4	18.3	58.6	22.7	100
3 months after vaccination	< 5 mm	0	0	5	39	44
	6~9 mm	0	0	39	163	202
	>10 mm	0	0	1	4	5
	total {	0	0	45	206	251
	% {	0	0	17.9	82.1	100
6 months after vaccination	< 5 mm	0	0	0	44	44
	6~9 mm	0	0	0	202	202
	>10 mm	0	0	0	5	5
	total {	0	0	0	251	251
	% {	0	0	0	100	100

though these express the phases of the course of local reaction. The percentage of scar was 22.7% at 1 month, 82.1% at 3 months and almost 100% at 6 months after vaccination. Most of the diameter of scar was less than 9 mm. As to the treatment of ulcer the expose under sun light and desinfection were done to prevent the secondary infection. Antituberculous drugs were not employed.

Discussion

The accelerated and augmented reaction at the repeated site was also observed at 6 (the second repetition) and 12 months (the third repetition) after BCG vaccination as had been at 3 months.

Terada⁶⁾ and Masumura⁷⁾ reported, tracing the process of the reaction, that the reaction became to disappear more rapidly with repetition and this tendency was more remarkable in induration than in redness. Bachi⁸⁾ compared the reactions of the second and the third repetitions histologically and reported that in the third repetition the increase in the earlier stage and the decrease in the successive stage of the inflammatory reaction became stronger than in the second repetition.

As it has been mentioned above, the "L" reaction is the change of color tone which is observed just before the disappearance of the reaction in relation to the accelerated reaction. Therefore, from the previous and present investigations the remarkable increase of the percentage of "L" reaction at the second repetition compared to the first and, moreover, the increase of the difference of the induration rate in 48 hour readings between the new and repeated sites imply the intensification of the grade of the acceleration by the repetition, although little difference was observed between the results of the first and the second repetition in the comparison of 24 hour value to 48 hour at the repeated site.

As the number of cases having larger diameter of redness at the repeated site than at the new site increased from the first to the second repetition (Fig. 5, and Fig. 9 in the previous report¹⁾), it may be said that the grade of augmentation also intensified. But, from the Table 1, and Table 3 in the previous report¹⁾, this tendency is not clear, perhaps because the influence of accelerated reaction is more remarkable in induration than in redness.

Therefore, it may be concluded that the grade of acceleration and augmentation becomes more remarkable from the first to the second repetition.

Little difference was observed between the results of the second and the third repetition, except the slight decrease of the number of cases having larger diameter of redness at the repeated site than at the new site in the third repeti-

tion and from this result it may be explained that the grade of augmentation begins to decrease after the second repetition. But the further investigations should be done following up the tuberculin tests for this conclusion.

When the results of the new sites of 6 and 12 months after BCG vaccination were compared to those of the previous report (1 and 3 months), the number of cases of which reaction at 24 hour was stronger than 48 hour increased in 6 and 12 months examination to a certain extent. And as the 12 month' test was done on the right upper arm far from the injection sites of the previous tests, it could not be considered that this phenomenon was due to the accelerated reaction. Future investigations are necessary for the significance of this phenomenon.

There are some investigations on the differential criterion to find out the positive conversion caused by the infection of virulent tubercle bacilli in BCG vaccinated groups from that caused by BCG vaccination alone⁹⁾¹⁰⁾¹¹⁾. But, as seen in Fig. 12, there is a considerable difference between the new and repeated sites and the present results are markedly higher in both positive and induration rate than the preceeding investigations⁹⁾¹⁵⁾. Therefore, these criteria should be corrected on the basis of the present and the future investigations.

On the change of color tone of the reaction "L" color tone was scarcely observed at the new site but in markedly high percentage at the repeated site. Saito et al.²⁾ reported previously that "L" reaction was possibly a specific but weak reaction appeared in relation to the frequent repetition of tuberculin test. Originally "L" reaction was apprehended as the reaction difficult to read and so only "L" color tone without induration was dealt with "L" reaction. But there are various grades of induration with the same color tone and it is impossible to draw a line between them. In the tuberculous patients "L" color tone also appeared with lapse of time at the new site and was understood as the change of color tone just before the disappearance of the reaction. Therefore, the reaction disappears more rapidly at the repeated site in consequence of acceleration and it is just before the disappearance of the reaction at 48 hour reading. In such a case the reaction is observed as the "L" reaction. According to this understanding, it may be natural to say that the "L" reaction is observed more in positive children caused by BCG vaccination than in those caused by the infection of virulent tubercle bacilli even at the repeated site, because the intense reaction continues for a long time and "L" color tone scarcely appears at 48 hours. In the weak and short continued reaction, it is possible that "L" color tone is observed at 48 hour even at the new site. Therefore, it may be said that the reaction which presents "L" color tone at 48 hours is generally weaker

but it should be mentioned that "L" color tone itself is not essentially related to the intensity of the reaction.

The ulcer and scar in BCG vaccinated site are a impediment to the wide spread of BCG in our country. Saito et al.¹²⁾ reported that the ulceration rate was about the same as usual BCG vaccine but the positive conversion rate of tuberculin reaction was very low by means of the vaccination of the heat-killed BCG vaccine. Obayashi¹³⁾¹⁴⁾ reported that there was a positive correlation between the viable units of BCG vaccine, positive conversion rate of tuberculin reaction and the local reaction on the BCG vaccinated site to a certain extent. Although this correlation is not so strong in individuals, the scar after BCG vaccination is inevitable at this stage. Therefore, we should endeavor to cure the ulcer as soon as possible and to leave the scar as small as possible. For this purpose it is necessary that BCG vaccination is not done to persons who maintain tuberculin allergy, BCG vaccine is injected as shallow as possible and the secondary infection to ulcer is prevented. From the present investigation, it is thought as satisfactory that the rate of scar was 80% in 3 months and 100% in 6 months after vaccination and about 95% of scar was less than 9 mm in diameter, in spite of the fact that the high tuberculin allergy was acquired in this group.

Summary

Continued from the previous report, tuberculin reaction was examined 6 and 12 months after BCG vaccination (the second and the third repetition at the repeated site, respectively).

1) Accelerated and augmented reaction was also remarkably observed in the second and the third repetition.

2) In the second repetition the grade of acceleration and augmentation became stronger than the first repetition. Subsequent process is now under investigation.

3) The positive rate in redness was lower but the induration rate was conversely higher about 20% at the new site than at the repeated site on and after the second repetition.

4) The reaction of which color tone was not fresh red as had formerly been seen but differently colored (for example, livid red, pale brown or only pigmentated and so on) and the margin of the reacted area was not discernible from the unreacted area was named as "L" reaction. The appearance rate of "L" reaction increased rapidly at the second repetition compared to the first and more than 90% of the reaction had "L" color tone.

5) It may be considered that "L" reaction is specific and related to the

acceleration in reaction in consequence of the repetition of the tuberculin reaction; that is, "L" color tone appears just before the tuberculin reaction decreases and then disappears with lapse of time and at the repeated site it is observed as early as at 48 hours because the accelerated tuberculin reaction disappears faster. Accordingly, the reactions in which "L" color tone is observed at 48 hours are generally weak, but "L" color tone itself is not essentially related to the intensity of the reaction.

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Note: Except for No. (1) all references are in Japanese.